ORIGINAL ARTICLE

Complicated appendicitis: Risk factors and outcomes of laparoscopic appendectomy – Polish laparoscopic appendectomy results from a multicenter, large-cohort study

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ABSTRACT

BACKGROUND: Preoperative classification of complicated and uncomplicated appendicitis (AA) is challenging. However, the differences in surgical outcomes necessitate the establishment of risk factors in developing, complicated AA. This study was an analysis of the clinical outcomes of laparoscopic appendectomies (LA), as well as preoperative risk factors for the development of complicated AA.

METHODS: The data of 618 patients who underwent LA in 18 surgical units across Poland and Germany were collected in an online web-based database created by the Polish Videosurgery Society. The surgical outcomes of patients with complicated and uncomplicated appendicitis were compared. Uni- and multivariate logistic regression models were used to establish risk factors for the development of complicated appendicitis.

RESULTS: In all, 1269 (27.5%) patients underwent LA for complicated appendicitis (Group 1) and 3349 (72.5%) for uncomplicated appendicitis (Group 2). The conversion rate, number of intra-operative adverse events, re-intervention rate, postoperative complications, and readmission rate was greater in Group 1. The preoperative risk factors associated with complicated appendicitis were: female sex (Odds ratio [OR]: 1.58), obesity (OR: 1.51), age >50 years (OR: 1.51), symptoms >48 hours (OR: 2.18), high Alvarado score (OR: 1.29 with every point), and C-reactive protein level >100 mg/L (OR: 3.92).

CONCLUSION: Several demographic and clinical risk factors for complicated AA were identified. LA for complicated appendicitis was associated with poorer outcomes.

Keywords: Acute appendicitis; complicated appendicitis; laparoscopic appendectomy.

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INTRODUCTION

Acute appendicitis (AA) is among the most common surgical emergencies, with a reported lifetime incidence of 8%.[1] It can be divided into two main categories: uncomplicated and complicated AA (e.g., gangrenous appendicitis, perforated appendix with or without phlegmon or abscess).[2,3] The proportion of complicated AA varies, and it can reach up to 50% in some reports.[4–8] Presence of complicated appendicitis is an independent risk factor of developing intraabdominal abscesses after laparoscopic appendectomy (LA).[9] Several previously published studies showed that LAs are feasible and beneficial, producing a shorter length of stay (LOS), reduced pain, decreased surgical site infection rate, shorter postoperative ileus, and a better cosmetic effect.[10,11] Moreover, LA has been shown to be safer in complicated AA than in open surgery; therefore, its use in the emergency setting is rising.[12–16] While challenging, discrimination between uncomplicated and complicated AA is clinically relevant as outcomes vary, with complicated cases faring worse.[17] Additionally, patients with uncomplicated AA may be successfully treated with antibiotics, in comparison to complicated cases, which practically always require an appendectomy.[18] Lastly, there is an ongoing debate as to whether LAs are beneficial to patients with complicated AA, due to a potentially higher risk of intraabdominal abscesses.[10]

MATERIALS AND METHODS

Aim

This study aims to identify the preoperative risk factors for complicated AA, and determine whether the outcomes of LA differ between uncomplicated and complicated AA.

Study Design

The multicenter observational study was performed in 18 surgical centers, 17 Polish and 1 German, over a 6-month period from October 2017 to March 2018. Data from patients undergoing LAs were collected in a web-based database. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used in the design and implementation of the study and to prepare the manuscript.[19] The study included data from patients operated on during the data collection period together with retrospective data from previous patients in each center. The coordinating surgeon and the local team of nurses, anesthesiologists, and assistants were responsible for data acquisition. The following variables were recorded in the database: annual number of LAs performed in each participating center, patient characteristics (sex, age, body mass index (BMI), ASA score, history of smoking, diabetes mellitus, timing from onset of symptoms to surgery, Alvarado score[20]), white blood cell count (WBC), C-reactive protein level (CRP), operative parameters (operative time, type of surgeon performing the appendectomy (resident/specialist), type of AA (uncomplicated/complicated), intraoperative adverse events, and postoperative outcomes (postoperative morbidity, need for surgical reintervention, length of hospital stay, need for 30-day readmission).

Based on whether their AA was complicated, patients were divided into two groups. Complicated AA was determined by the presence of gangrenous appendicitis or perforated appendix with or without abscess. The diagnosis of complicated AA was based on intraoperative and pathological visualization of the appendix.

For the purpose of this study, no changes in treatment were implemented. The study was monitored by a primary investigator who processed and verified any missing or unclear data submitted to the central database. The project was supported by the Videosurgery Chapter of the Association of Polish Surgeons. The data was completely anonymized, and the website collected no patient identification data. The only hospital data included in the survey was the annual number of LAs performed. Since the study was observational in nature, informed consent and formal approval by a local ethics committee were not required.

Statistical Analysis

Statistical analyzes were done using Statsoft STATISTICA 13.0 PL (Statsoft Inc., Tulsa, Oklahoma, USA). Continuous variables were presented using means with standard deviations (SD) or medians with inter-quartile ranges (IQR) for skewed variables. Then, comparisons between groups were done using t-student tests for normally distributed variables and Mann–Whitney's tests for skewed variables. Depending on the quantities in the subgroups, the dichotomous variables were included in chi-squared Pearson's, Yates', and Fisher's exact tests. Finally, univariate and multivariate logistic regression models were built to determine risk factors for postoperative complications. Results were considered statistically significant when p-values were <0.05. In case of missing data, pairwise deletion was used.

RESULTS

The study included 4618 patients. The mean number of patients included per center was 256 (range 103–648). A total of 1349 patients were operated on in centers with an annual volume of <50 LAs per year, and 3269 with an annual volume of >50. Of total, 2419 (52.38%) patients were male, and 2199 (47.61%) were female. The median age of the entire study group was 33 years. The median BMI was 24.8. A total of 793 (17.17%) patients were active smokers, whereas 149 (3.23%) had diabetes mellitus. Total 3210 (69.51%) patients had ASA class 1, 1216 (26.33%) ASA class 2, 185 (4.01%) ASA class 3, and 7 (0.15%) ASA class 4. A total of 1458 (31.57%) patients presented with symptoms of AA >48 h before surgery. Median WBC was 13.1 mm^3 and CRP was 27.3 mg/l.

A total of 1269 (27.48%) patients were diagnosed with complicated AA and 3349 patients (72.52%) with uncomplicated AA. An unchanged appendix was found in 371 (8.03%) patients. Baseline characteristics of these two groups are shown in Table 1. Apart from smoking history, statistical differences were present in all analyzed parameters (Table 1).

Table 2 shows the differences in operative parameters between groups. Patients with complicated AA were more often operated on by senior surgeons, with differences in technique of appendiceal stump closure, use of postoperative drainage, and intraoperative adverse events.

Overall 118 (9.3%) patients in the complicated group and 98 (2.93%) in the uncomplicated group were diagnosed with postoperative complications (p<0.001). There were also differences in their severity according to the Clavien–Dindo classification. Fifty-three (4.18%) patients in the complicated group and forty-five (1.34%) in the uncomplicated group required reintervention after LA, mostly due to intraabdominal abscesses (51 cases). Median LOS was longer in the complicated group (4 vs. 3 days, p<0.001). Readmission was more common in the complicated group (48 (3.76%) vs. 71 (2.12%), p=0.003) (Table 2).

The results of the univariate analysis for complicated appendicitis utilizing preoperative parameters are shown in Table 3. In the multivariate model, only female sex (OR 1.58, 95% CI 1.14–2.17), obesity (OR 1.51, 95% CI 1.02–2.23), the time from onset of symptoms to surgery (OR 2.18, 95% CI 1.57–3.03), Alvarado score (OR 1.29, 95% CI 1.19–1.39 with every point higher), and CRP >100 mg/l (OR 3.92, 95% CI 2.75–5.58) remained significant (Table 3).

DISCUSSION

Based on the findings from this multicenter cohort study, we identified several risk factors for the development of complicated AA. Once AA becomes complicated, we confirmed a greater risk for adverse outcomes. For years, perforated/gangrenous AA has been considered just an advanced state of AA.[21] After much debate, it was concluded that complicated and uncomplicated AA, in fact, have different pathophysiology.[22,23] This conclusion came from several North-European trials that showed the feasibility of non-operative management in uncomplicated appendicitis, even when symptoms had been present for long periods of time.[24–27] In comparison, conservative treatment of complicated AA has very high failure rates, with surgeons in agreement on the need for surgical intervention.[23] Unfortunately, to distinguish between complicated and uncomplicated AA is challenging. The gold standard is various imaging studies, predominantly CT.[28] However, this modality is not possible in all surgical centers worldwide. Where available, it is not routinely used when

Table 1. Demographic characteristics of studied groups

	Complicated	Noncomplicated	p
No, n (%)	1269 (27.48)	3349 (72.52)	n/a
Males/females, n (%)	711/558 (56/44)	1708/1641 (51/49)	0.001[1]
Median age, years (IQR)	40 (28–57)	30 (23–42)	<0.001[2]
Age >50 years, n (%)	418 (32.94)	569 (17)	<0.001[1]
Median body mass index, kg/m^2 (IQR)	26.3 (22.9–30)	24.5 (21.9–27.8)	<0.001[1]
Obesity (body mass index >25 kg/m^2), n (%)	314 (24.71)	513 (15.31)	<0.001[1]
ASA class, n (%)			
I	772 (60.80)	2438 (72.82)	<0.001[1]
II	419 (32.99)	797 (23.80)	
III	77 (6.09)	108 (3.21)	
IV	1 (0.11)	6 (0.17)	
Smoking, n (%)	236 (18.58)	557 (16.62)	0.188
Diabetes mellitus, n (%)	74 (5.87)	75 (2.23)	<0.001[1]
Symptoms >48 h vs. <48 h, n (%)	548 (43.21)	910 (27.16)	<0.001[1]
Median Alvarado score (IQR)	7 (5–8)	6 (4–7)	<0.001[2]
Median white blood cell count, *1000 per mm^3 (IQR)	14.3 (11.5–17.32)	12.6 (9.5–15.68)	<0.001[2]
Leukocytosis >20.000/mm^3, n (%)	174 (13.72)	249 (7.44)	<0.001[1]
Median C-reactive protein, mg/l (IQR)	74.35 (25.2–155.18)	20 (4.6–51.6)	<0.001[2]
C-reactive protein >100 mg/l, n (%)	497 (39.17)	363 (10.83)	<0.001[1]

[1]Pearson's chi-square test; [2]Mann-Whitney's test. IQR: Inter-quartile ranges; ASA: American Society of Anesthesiologists.

Table 2. Differences in operative parameters between groups

	Complicated	Noncomplicated	p
No, n (%)	1269 (27.48)	3349 (72.52)	n/a
Annual volume, lap. appendectomies per year, n (%)			
>50	979 (77.15)	2290 (68.38)	<0.001
<50	290 (22.85)	1059 (31.62)	
Residents vs. specialists, n (%)	520/749 (41/59)	1507/1842 (45/55)	0.005
Median operative time, min (IQR)	60 (45–85)	50 (35–65)	<0.001
Technique of closing appendiceal stump, n (%)			
Clipping	637 (50.20)	2209 (65.99)	<0.001
Suturing/ligature	222 (17.49)	230 (6.86)	
Stapler	153 (12.06)	158 (4.73)	
Endoloop	140 (11.03)	467 (13.90)	
Röder loop	117 (9.22)	285 (8.51)	
Intraoperative adverse events, n (%)	64 (5.05)	42 (1.26)	<0.001
Conversion rate, n (%)	212 (16.74)	89 (2.65)	<0.001
Postoperative drainage, n (%)	1163 (91.67)	2340 (69.90)	<0.001
Perioperative morbidity, n (%)	118 (9.30)	98 (2.93)	<0.001
Clavien-Dindo classification of surgical complications, n (%)			
V	3 (0.24)	0	0.011
IV	2 (0.16)	2 (0.06)	
III	44 (3.47)	33 (0.99)	
II	37 (2.92)	37 (1.10)	
I	28 (2.21)	24 (0.72)	
Reinterventions after primary procedure, n (%)	53 (4.18)	45 (1.34)	<0.001
Median length of stay	4	3	
(IQR)	(3–6)	(2–4)	
(Range)	(0–60)	(0–61)	<0.001
Readmission rate, n (%)	48 (3.76)	71 (2.12)	0.003

IQR: Inter-quartile ranges.

diagnosing every lower right quadrant pain presenting in the emergency department. Although there are several scoring systems that are based on clinical characteristics and laboratory tests, they have limited accuracy.[20,29–31]

The incidence of complicated AA (27.5%) in this cohort is in the range of previously published reports.[6–8,32–34] When adjusting for confounding variables, we observed that female sex was associated with a higher rate of complicated AA. This was surprising because the majority of published studies did not find an association between patients' sex and the rate of complicated AA.[35–37] Additionally, we confirmed that patients with complicated AA are, overall, older. A possible explanation for this observation was previously described. Andersson and Luckmann found that the incidence of complicated appendicitis is constant during one's lifetime, whereas the incidence of uncomplicated AA varies with age and is highest in younger individuals.[23,38] The relatively low incidence of uncomplicated AA in the elderly may explain the subsequent rise in the mean age of patients in the complicated AA group.[23,38] A further risk factor observed was diabetes; the altered gastrointestinal neurohumoral functioning and impaired host immunity in patients with diabetes result in severe courses of various acute gastrointestinal diseases.[36,39,40] Patients with diabetes with uncomplicated AA had a higher rate of failure when treated conservatively, often needing appendectomies.[41] Similarly, obesity might conceal physical symptoms of AA, leading to delay of diagnosis what may explain the relationship between complicated AA and obesity as one of the risk factors.[42]

The relationship between the time from symptom onset and the risk of developing complicated AA has to be interpreted with caution. On one hand, the aforementioned studies demonstrated that complicated AA is not just a late stage of AA. In contrast, several well-designed trials clearly

Table 3. Risk factors for intraoperative diagnosis of complicated appendicitis

	OR	95% CI	p
Univariate			
Females vs. males	1.25	1.09–1.42	0.001
Age >50 years	2.40	2.07–2.78	<0.001
Obesity (BMI >30 kg/m^2)	1.82	1.45–2.27	<0.001
ASA class	1.55	1.36–1.77	<0.001
Diabetes mellitus	2.73	1.93–3.86	<0.001
Symptoms >48 h vs. <48 h	2.04	1.75–2.38	<0.001
With every point of Alvarado grading higher	1.24	1.19–1.29	<0.001
Leukocytosis >20.000/mm^3	1.98	1.60–2.45	<0.001
C-reactive protein >100 mg/l	5.30	4.41–6.38	<0.001
Multivariate			
Females vs. males	1.58	1.14–2.17	0.005
Age >50 years	1.51	0.98–2.33	0.059
Obesity (BMI >30 kg/m^2)	1.51	1.02–2.23	0.039
ASA class	1.15	0.83–1.57	0.401
Diabetes mellitus	1.06	0.50–2.26	0.879
Symptoms >48 h vs. <48 h	2.18	1.57–3.03	<0.001
With every point of Alvarado grading higher	1.29	1.19–1.39	<0.001
Leukocytosis >20.000/mm^3	1.68	0.97–2.92	0.062
C-reactive protein >100 mg/l	3.92	2.75–5.58	<0.001

OR: Odds Ratios; CI: Confidence interval; BMI: Body mass index; ASA: American Society of Anesthesiologists.

showed the relationship between duration of symptoms and complicated AA.[43–45] For instance, Bickell et al.[46] noted that the risk of appendiceal perforation increased by 5% for each ensuing 12-h period after 36 h. Augustin et al.[44] observed perforation even earlier, at less than 12 h after symptom onset. On the contrary, a study by Kim et al.[47] comprising more than 4000 patients did not find any association between the time elapsed between evaluation in the emergency room and the appendectomy. Our data clearly demonstrated that timing matters, with a longer duration from symptom onset, indeed, being a risk factor for complicated AA. Another factor analyzed was CRP. Our data showed that, similar to other studies, patients with complicated AA had greater CRP values.[32,48] Lastly, higher Alvarado scores were, in our opinion, derivatives from symptoms of abscess peritonitis such as ileus, fever, anorexia, and rebound tenderness.

The most clinically relevant finding was that, once complicated, AA is associated with significantly worse outcomes. Practically all measured perioperative and postoperative parameters significantly tilted against the complicated AA group. Operative time, conversions, and intraoperative adverse events clearly showed that LAs for complicated AA are more difficult. It is, therefore, not surprising that the rate of senior surgeons performing the surgery and the use of more sophisticated techniques for appendiceal stump closure is higher in this group. There were also differences in postoperative outcomes in the complicated group. Patients suffered from higher morbidity (the only mortality occurred in this group), prolonged LOS, and more readmissions.

Similar to other observational multicenter reports, our study does have certain limitations. Firstly, a large number of patients were retrospectively included. We could not accurately analyze each participating center's perioperative protocol, such as antibiotic regimens or discharge criteria. As shown in other large observational studies, there is significant variability in the management of AA among surgical centers.[49] Secondly, the readmission percentage in our data only represents readmissions to the original surgical department, instead of the overall rate to other departments or hospitals, allowing for underestimation of the true readmission rate. According to other national studies, readmission rates can be slightly higher than reported in our analysis.[50] However, the readmission statistics are combined from all study groups, so the bias is thought to be reduced. Thirdly, the resident/senior surgeon ratio was different between groups. We do not believe this seriously biased the results, since the varying ratios between centers, while statistically significant, were not that large. Additionally, it was seen that LAs performed by residents under supervision, in fact, resulted in similar outcomes.[51] Lastly, the final limitation was the observed differences in appendiceal stump closure between groups. We were not able to provide data on the rationale for using any particular method of stump closure, for example endostapler vs. endoloop/clip; however, it is likely that the decision was based on the surgeon's discretion and intraoperative findings.

Conclusions

Based on the results of this cohort study, we concluded that LAs for complicated appendicitis are associated with significantly worse perioperative outcomes. In addition, we identified older age, female sex, obesity, diabetes mellitus, high CRP, and higher Alvarado scores as preoperative risk factors that suggest a higher risk of developing complicated AA. For this reason, patients with these factors should be considered for surgery before conservative treatment.

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All authors would like the names of the individual members of the collaboration group to be searchable through their individual PubMed records.

Ethics Approval and Consent to Participate in the Study

The study was observational in nature, and the approval by the local ethics committee of Jagiellonian University, Krakow,

Poland has been obtained for conducting this study. The data was completely anonymized, and no patient or hospital information was collected in the database. The study protocol was approved by the board of the Videosurgery Chapter of the Association of Polish Surgeons, and the study was conducted under its supervision. All procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (Fortaleza).

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ORİJİNAL ÇALIŞMA - *ÖZET*

Komplike apandisit: Laparoskopik apandektominin risk faktörleri ve sonlanımları – çok merkezli geniş çaplı Pol-LA kohort çalışmasının (Polonya Laparoskopik Apandektomi) sonuçları

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AMAÇ: Komplike olan ve olmayan akut apandisitin (AA) ameliyat öncesi sınıflandırılması zordur. Ancak cerrahi sonuçlardaki farklılıklar komplike AA'nın gelişimindeki risk faktörlerinin belirlenmesini zorunlu kılmaktadır. Laparoskopik apandektomilerin (LA) klinik sonuçlarını inceledik ve komplike AA'nın gelişmesine ilişkin ameliyat öncesi risk faktörlerini saptadık.

GEREÇ VE YÖNTEM: Polonya ve Almanya'da 18 cerrahi birimde LA uygulanan 4618 hastanın verileri Polonya Videocerrahi Derneği tarafından oluşturulan sanal veri tabanında toplandı. Komplike olan ve olmayan hastaların cerrahi sonuçları karşılaştırıldı. Komplike apandisit gelişmesine ilişkin risk faktörlerini belirlemek için tek ve çok değişkenli regresyon modelleri kullanıldı.

BULGULAR: Komplike apandisiti olan 1269 (%27.5) (Grup 1) ve olmayan (Grup 2) 3349 (%72.5) hasta LA oldu. Cerrahiye geçiş oranı, ameliyat sırasında advers etkiler, yeniden girişim oranı, ameliyat sonrası komplikasyonlar ve yeniden hastaneye kabul oranları Grup 1'de daha yüksekti. Komplike apandisitle ilişkili ameliyat öncesi risk faktörleri kadınlarda (OR 1.58), obezite (OR 1.51), yaş >50 yıl (OR 1.51), semptomlar >48 saat içinde (OR 2.18), daha yüksek Alvarado skoru (OR her noktada 1.29) ve CRP >100 mg/l (OR 3.92) idi.

TARTIŞMA: Komplike AA için birkaç demografik ve klinik risk faktörü tanımlanmıştır. Komplike apandisit için uygulanan LA daha kötü sonlanımlarla ilişkiliydi.

Anahtar sözcükler: Akut apandisit; komplike apandisit; laparoskopik apandektomi.

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